# Clinical trial results:
# An Open Label, Intravenous to Oral Switch, Multiple Dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Voriconazole in Immunocompromised Children Aged 2 to Below 12 Years who are at High Risk for Systemic Fungal Infection

## Summary

| | |
|---|---|
| EudraCT number | 2012-001133-14 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 26 October 2009 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 23 May 2016 |
| First version publication date | 22 July 2015 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | A1501088 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00739934 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Pfizer, Inc. |
| Sponsor organisation address | 235 East 42nd Street, New York, United States, NY 10017 |
| Public contact | Pfizer ClinicalTrials.gov Call Center<br>, Pfizer, Inc., +1 8007181021,<br>ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center<br>, Pfizer, Inc., +1 8007181021,<br>ClinicalTrials.gov_Inquiries@pfizer.com |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-000191-PIP01-08 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 23 March 2010 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 26 October 2009 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To characterize the pharmacokinetics of voriconazole following an intravenous (IV) to oral switch regimen in immunocompromised children aged 2 to below 12 years who were at high risk for systemic fungal infection.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 09 December 2008 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 40 |
| Worldwide total number of subjects | 40 |
| EEA total number of subjects | 0 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 40 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Subjects were recruited from 11 centers in United States. Study was started from 09 Dec 2008 and completed on 26 Oct 2009.

### Period 1

| | |
|---|---|
| Period 1 title | Baseline period |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | All Subjects |

Arm description:

Voriconazole intravenous (IV) dosing regimen was administered on Days 1 to 7 (up to Day 20 or more if clinically indicated). The oral maintenance dosing regimen was administered following voriconazole IV and lasted 6.5 days (up to Day 30 if clinically indicated).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Voriconazole |
| Investigational medicinal product code | |
| Other name | Vfend |
| Pharmaceutical forms | Infusion, Oral suspension |
| Routes of administration | Oral use, Intravenous use |

Dosage and administration details:

Voriconazole IV dosing regimen (7 mg/kg every 12 hours) was administered in the morning and evening on Days 1 to 7 (up to Day 20 or more if clinically indicated)
with a maximum infusion rate of 3 mg/kg/hr. The oral maintenance dosing regimen (200 mg every 12 hours) was administered following voriconazole IV in the morning and evening and lasted 6.5 days (up to Day 30 if clinically indicated).

| **Number of subjects in period 1** | All Subjects |
|---|---|
| Started | 40 |
| Completed | 40 |

### Period 2

| | |
|---|---|
| Period 2 title | Voriconazole IV |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

## Arms

| **Arm title** | Voriconazole IV |
|---|---|

Arm description:

Voriconazole IV doses were administered.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Voriconazole |
| Investigational medicinal product code | |
| Other name | Vfend |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Voriconazole IV dosing regimen (7 mg/kg every 12 hours) was administered in the morning and evening on Days 2 to 7 (up to Day 20 or more if clinically indicated)
with a maximum infusion rate of 3 mg/kg/hr.

| **Number of subjects in period 2** | Voriconazole IV |
|---|---|
| Started | 40 |
| Completed | 34 |
| Not completed | 6 |
| Adverse Event | 6 |

## Period 3

| | |
|---|---|
| Period 3 title | Voriconazole Oral |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

## Arms

| **Arm title** | Voriconazole Oral |
|---|---|

Arm description:

Voriconazole oral doses were administered following voriconazole IV.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Voriconazole |
| Investigational medicinal product code | |
| Other name | Vfend |
| Pharmaceutical forms | Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

The oral maintenance dosing regimen (200 mg every 12 hours) was administered following voriconazole IV in the morning and evening and lasted 6.5 days (up to Day 30 if clinically indicated).

| **Number of subjects in period 3** | Voriconazole Oral |
|---|---|
| Started | 34 |
| Completed | 31 |
| Not completed | 3 |
| Unspecified | 3 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Baseline period |

Reporting group description: -

| Reporting group values | Baseline period | Total | |
|---|---|---|---|
| Number of subjects | 40 | 40 | |
| Age categorical<br>Units: Subjects | | | |
| 2 to less than (<) 6 years | 24 | 24 | |
| 6 to <12 years | 16 | 16 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 17 | 17 | |
| Male | 23 | 23 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | All Subjects |
| Reporting group description: | |
| Voriconazole intravenous (IV) dosing regimen was administered on Days 1 to 7 (up to Day 20 or more if clinically indicated). The oral maintenance dosing regimen was administered following voriconazole IV and lasted 6.5 days (up to Day 30 if clinically indicated). | |
| Reporting group title | Voriconazole IV |
| Reporting group description: | |
| Voriconazole IV doses were administered. | |
| Reporting group title | Voriconazole Oral |
| Reporting group description: | |
| Voriconazole oral doses were administered following voriconazole IV. | |

### Primary: Area Under the Curve Over Dosing Interval at Steady State (AUC12,ss) Following IV Administration

| | |
|---|---|
| End point title | Area Under the Curve Over Dosing Interval at Steady State (AUC12,ss) Following IV Administration[1] |
| End point description: | |
| AUC12,ss = Area under the plasma concentration-time profile from time zero (predose) to twelve hours at steady-state. AUC12,ss was obtained by the Linear or Log trapezoidal method. This analysis included the intent-to-treat (ITT) population– subjects who had completed PK blood sampling for at least one day. | |
| End point type | Primary |
| End point timeframe: | |
| Day 7 (up to Day 20 or more) at predose, 60 and 138 minutes, 4, 6, 8 and 12 hours postdose | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

| End point values | Voriconazole IV | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 36[2] | | | |
| Units: microgram*hour per milliliter (µg*h/mL) | | | | |
| geometric mean (standard deviation) | 21.42 (± 35.05) | | | |

Notes:

[2] - N = number of subjects with analyzable data.

### Statistical analyses

No statistical analyses for this end point

### Primary: Peak Plasma Concentration at Steady State (Cmax,ss) Following IV Administration

| | |
|---|---|
| End point title | Peak Plasma Concentration at Steady State (Cmax,ss) Following IV Administration[3] |

End point description:

This analysis included the ITT population- subjects who had completed PK blood sampling for at least one day.

| End point type | Primary |
|---|---|

End point timeframe:

Day 7 (up to Day 20 or more) at predose, 60 and 138 minutes, 4, 6, 8 and 12 hours postdose

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

| **End point values** | Voriconazole IV | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 36[4] | | | |
| Units: µg/mL | | | | |
| geometric mean (standard deviation) | 4.26 (± 3.73) | | | |

Notes:

[4] - N = number of subjects with analyzable data.

## Statistical analyses

No statistical analyses for this end point

## Primary: Time to Reach Cmax (Tmax) Following IV Administration

| End point title | Time to Reach Cmax (Tmax) Following IV Administration[5] |
|---|---|

End point description:

This analysis included the ITT population- subjects who had completed PK blood sampling for at least one day.

| End point type | Primary |
|---|---|

End point timeframe:

Day 7 (up to Day 20 or more) at predose, 60 and 138 minutes, 4, 6, 8 and 12 hours postdose

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

| **End point values** | Voriconazole IV | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 36[6] | | | |
| Units: hours | | | | |
| median (full range (min-max)) | 2.3 (1 to 4.07) | | | |

Notes:

[6] - N = number of subjects with analyzable data.

## Statistical analyses

No statistical analyses for this end point

## Primary: AUC12,ss Following Oral Administration

| End point title | AUC12,ss Following Oral Administration[7] |
|---|---|

End point description:

AUC12,ss = Area under the plasma concentration-time profile from time zero (predose) to twelve hours at steady-state. AUC12,ss was obtained by the Linear or Log trapezoidal method. This analysis included the ITT population- subjects who had completed PK blood sampling for at least one day.

| End point type | Primary |
|---|---|

End point timeframe:

Day 7 (or later) predose, 1, 2, 4, 6, 8 and 12 hours postdose

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

| **End point values** | Voriconazole Oral | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 33[8] | | | |
| Units: µg*h/mL | | | | |
| geometric mean (standard deviation) | 18.64 (± 50.63) | | | |

Notes:

[8] - N = number of subjects with analyzable data.

### Statistical analyses

No statistical analyses for this end point

### Primary: Cmax,ss Following Oral Administration

| End point title | Cmax,ss Following Oral Administration[9] |
|---|---|

End point description:

This analysis included the ITT population- subjects who had completed PK blood sampling for at least one day.

| End point type | Primary |
|---|---|

End point timeframe:

Day 7 (or later) predose, 1, 2, 4, 6, 8 and 12 hours postdose

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

| **End point values** | Voriconazole Oral | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 33[10] | | | |
| Units: µg/mL | | | | |
| geometric mean (standard deviation) | 3.62 (± 4.66) | | | |

Notes:

[10] - N = number of subjects with analyzable data.

### Statistical analyses

No statistical analyses for this end point

## Primary: Tmax Following Oral Administration

| End point title | Tmax Following Oral Administration[11] |
|---|---|

End point description:

This analysis included the ITT population- subjects who had completed PK blood sampling for at least one day.

| End point type | Primary |
|---|---|

End point timeframe:

Day 7 (or later) predose, 1, 2, 4, 6, 8 and 12 hours postdose

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned to be reported for this endpoint.

| End point values | Voriconazole Oral | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 33[12] | | | |
| Units: hours | | | | |
| median (full range (min-max)) | 1.07 (0.73 to 8.03) | | | |

Notes:

[12] - N = number of subjects with analyzable data.

### Statistical analyses

No statistical analyses for this end point

## Secondary: AUC12 Following an IV Loading Dose

| End point title | AUC12 Following an IV Loading Dose |
|---|---|

End point description:

AUC12 = Area under the plasma concentration-time profile from time zero (predose) to twelve hours. AUC12 was obtained by the Linear or Log trapezoidal method. This analysis included the ITT population- subjects who had completed PK blood sampling for at least one day.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 1 predose, 60 and 138 minutes, 4, 6, 8 and 12 hours postdose

| End point values | Voriconazole IV | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 33[13] | | | |
| Units: µg*h/mL | | | | |
| geometric mean (standard deviation) | 7.85 (± 6.71) | | | |

Notes:

[13] - N = number of subjects with analyzable data.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Cmax Following an IV Loading Dose

| End point title | Cmax Following an IV Loading Dose |
|---|---|

End point description:

This analysis included the ITT population- subjects who had completed PK blood sampling for at least one day.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 1 predose, 60 and 138 minutes, 4, 6, 8 and 12 hours postdose

| **End point values** | Voriconazole IV | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 33[14] | | | |
| Units: µg/mL | | | | |
| geometric mean (standard deviation) | 2.15 (± 1.1) | | | |

Notes:

[14] - N = number of subjects with analyzable data.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Tmax Following an IV Loading Dose

| End point title | Tmax Following an IV Loading Dose |
|---|---|

End point description:

This analysis included the ITT population- subjects who had completed PK blood sampling for at least one day.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 1 predose, 60 and 138 minutes, 4, 6, 8 and 12 hours postdose

| **End point values** | Voriconazole IV | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 33[15] | | | |
| Units: hours | | | | |
| median (full range (min-max)) | 2.3 (1.72 to 4.08) | | | |

Notes:

[15] - N = number of subjects with analyzable data.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Trough Concentrations (Cmin)

| End point title | Trough Concentrations (Cmin) |
|---|---|

End point description:

This analysis included the ITT population- subjects who had completed PK blood sampling for at least one day. Here, n = number of subjects who contributed to data.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 7 (up to Day 20 or more) for IV; Day 7 (or later) for oral at predose

| **End point values** | All Subjects | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 36[16] | | | |
| Units: µg/mL | | | | |
| geometric mean (standard deviation) | | | | |
| IV Day 7 (up to Day 20) (n=36) | 0.61 (± 2.56) | | | |
| Oral Day 7 (up to Day 30) (n=32) | 0.52 (± 3.32) | | | |

Notes:

[16] - N = number of subjects with analyzable data

## Statistical analyses

No statistical analyses for this end point

## Secondary: AUC12,ss of N-oxide Voriconazole Metabolite (UK-121, 265) Following IV Administration

| End point title | AUC12,ss of N-oxide Voriconazole Metabolite (UK-121, 265) Following IV Administration |
|---|---|

End point description:

AUC12,ss = Area under the plasma concentration-time profile from time zero (predose) to twelve hours at steady-state. AUC12,ss was obtained by the Linear or Log trapezoidal method. This analysis included the ITT population- subjects who had completed PK blood sampling for at least one day.

| End point type | Secondary |
|---|---|

End point timeframe:

Days 1 and 7 (up to Day 20 or more) predose, 60 and 138 minutes, 4, 6, 8 and 12 hours postdose

| **End point values** | Voriconazole IV | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 39[17] | | | |
| Units: µg*h/mL | | | | |
| geometric mean (standard deviation) | | | | |
| Day 1 | 20.98 (± 8.05) | | | |
| Day 7 (up to Day 20) | 41.95 (± 14.3) | | | |

Notes:

[17] - N = number of subjects with analyzable data.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Cmax,ss of N-oxide Voriconazole Metabolite (UK-121, 265) Following IV Administration

| End point title | Cmax,ss of N-oxide Voriconazole Metabolite (UK-121, 265) Following IV Administration |
|---|---|

End point description:

This analysis included the ITT population- subjects who had completed PK blood sampling for at least one day.

| End point type | Secondary |
|---|---|

End point timeframe:

Days 1 and 7 (up to Day 20 or more) predose, 60 and 138 minutes, 4, 6, 8 and 12 hours postdose

| **End point values** | Voriconazole IV | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 39[18] | | | |
| Units: µg/mL | | | | |
| geometric mean (standard deviation) | | | | |
| Day 7 | 2.97 (± 0.94) | | | |
| Day 7 (up to Day 20) | 4.47 (± 1.44) | | | |

Notes:

[18] - N = number of subjects with analyzable data.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Tmax of N-oxide Voriconazole Metabolite (UK-121, 265) Following IV Administration

| End point title | Tmax of N-oxide Voriconazole Metabolite (UK-121, 265) Following IV Administration |
|---|---|

End point description:

Zero Tmax refers to the highest concentration observed for one subject at predose. The profile of the metabolite is relatively flat, which could result in slight variation in sample collection or assay process. This analysis included the ITT population- subjects who had completed PK blood sampling for at least one day.

| End point type | Secondary |
|---|---|

End point timeframe:

Days 1 and 7 (up to Day 20 or more) predose, 60 and 138 minutes, 4, 6, 8 and 12 hours postdose

| **End point values** | Voriconazole IV | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 39[19] | | | |
| Units: hours | | | | |
| median (full range (min-max)) | | | | |
| Day 1 | 4 (1.72 to 8) | | | |

| | | | | |
|---|---|---|---|---|
| Day 7 (up to Day 20) | 4 (0 to 12.05) | | | |

Notes:

[19] - N=number of subjects with analyzable data.

### Statistical analyses

No statistical analyses for this end point

## Secondary: AUC12,ss of N-oxide Voriconazole Metabolite (UK-121, 265) Following Oral Administration

| | |
|---|---|
| End point title | AUC12,ss of N-oxide Voriconazole Metabolite (UK-121, 265) Following Oral Administration |

End point description:

AUC12,ss = Area under the plasma concentration-time profile from time zero (predose) to twelve hours at steady-state. AUC12,ss was obtained by the Linear or Log trapezoidal method. This analysis included the ITT population- subjects who had completed PK blood sampling for at least one day.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Day 7 (or later) predose, 1, 2, 4, 6, 8 and 12 hours postdose

| **End point values** | Voriconazole Oral | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 33[20] | | | |
| Units: µg*h/mL | | | | |
| geometric mean (standard deviation) | 51.65 (± 27.88) | | | |

Notes:

[20] - N = number of subjects with analyzable data.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Cmax,ss of N-oxide Voriconazole Metabolite (UK-121, 265) Following Oral Administration

| | |
|---|---|
| End point title | Cmax,ss of N-oxide Voriconazole Metabolite (UK-121, 265) Following Oral Administration |

End point description:

This analysis included the ITT population- subjects who had completed PK blood sampling for at least one day.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Day 7 (or later) predose, 1, 2, 4, 6, 8 and 12 hours postdose

| End point values | Voriconazole Oral | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 33[21] | | | |
| Units: µg/mL | | | | |
| geometric mean (standard deviation) | 5.62 (± 2.54) | | | |

Notes:

[21] - N = number of subjects with analyzable data.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Tmax of N-oxide Voriconazole Metabolite (UK-121, 265) Following Oral Administration

| End point title | Tmax of N-oxide Voriconazole Metabolite (UK-121, 265) Following Oral Administration |
|---|---|

End point description:

This analysis included the ITT population- subjects who had completed PK blood sampling for at least one day.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 7 (or later) predose, 1, 2, 4, 6, 8 and 12 hours postdose

| End point values | Voriconazole Oral | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 33[22] | | | |
| Units: hours | | | | |
| median (full range (min-max)) | 3.97 (0.92 to 8.03) | | | |

Notes:

[22] - N = number of subjects with analyzable data.

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to 1 month after last dose of investigational product

Adverse event reporting additional description:

Same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non--serious in another subject.
EU BR specific AE tables were generated separately as per EU format using latest coding.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Voriconazole Oral |

Reporting group description:

Voriconazole oral maintenance dosing regimen (200 mg every 12 hours) was administered following voriconazole IV in the morning and evening and lasted 6.5 days (up to Day 30 if clinically indicated).

| | |
|---|---|
| Reporting group title | Voriconazole IV |

Reporting group description:

Voriconazole IV dosing regimen (7 mg/kg every 12 hours) was administered on Days 1 to 7 (up to Day 2 0 or more if clinically indicated).

| Serious adverse events | Voriconazole Oral | Voriconazole IV | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 13 / 34 (38.24%) | 6 / 40 (15.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alanine aminotransferase increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme increased | | | |

| | | | |
|---|---|---|---|
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cytomegalovirus test | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Transplant failure | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypotension | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venoocclusive disease | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Posterior reversible encephalopathy syndrome | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration | | | |

| | | | |
|---|---|---|---|
| site conditions | | | |
| Medical device complication | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device dislocation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 5 / 34 (14.71%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Graft versus host disease in skin | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Hypoxia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Cytomegalovirus infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterobacter bacteraemia | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterobacter sepsis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | Voriconazole Oral | Voriconazole IV | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 34 / 34 (100.00%) | 39 / 40 (97.50%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant mesenchymoma | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Vascular disorders | | | |
| Capillary leak syndrome | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Haemorrhage | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Hypotension | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 2 / 40 (5.00%) | |
| occurrences (all) | 1 | 2 | |
| Hypertension | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 11 / 34 (32.35%) | 13 / 40 (32.50%) | |
| occurrences (all) | 11 | 13 | |
| Venoocclusive disease | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Catheter site erythema | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Catheter site haemorrhage | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Catheter site pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Chest pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Chills | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Drug withdrawal syndrome | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 0 / 40 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Face oedema | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Facial pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gravitational oedema | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fatigue | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | 2 / 40 (5.00%) | |
| occurrences (all) | 3 | 2 | |
| Localised oedema | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Mucosal inflammation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 11 / 34 (32.35%) | 20 / 40 (50.00%) | |
| occurrences (all) | 11 | 24 | |
| Medical device complication | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oedema peripheral | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 4 / 34 (11.76%) | 7 / 40 (17.50%) | |
| occurrences (all) | 4 | 7 | |

| | | | |
|---|---|---|---|
| Pyrexia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 11 / 34 (32.35%) | 15 / 40 (37.50%) | |
| occurrences (all) | 11 | 19 | |
| Suprapubic pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Immune system disorders | | | |
| Engraftment syndrome | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 4 / 40 (10.00%) | |
| occurrences (all) | 2 | 4 | |
| Acute graft versus host disease in skin | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Graft versus host disease | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 4 / 34 (11.76%) | 3 / 40 (7.50%) | |
| occurrences (all) | 4 | 3 | |
| Multiple allergies | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Reproductive system and breast disorders | | | |
| Genital erythema | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Pelvic pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |

| | | | |
|---|---|---|---|
| Pruritus genital | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Apnoea | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Atelectasis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Epistaxis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 5 / 34 (14.71%) | 3 / 40 (7.50%) | |
| occurrences (all) | 5 | 4 | |
| Cough | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 3 / 40 (7.50%) | |
| occurrences (all) | 2 | 3 | |
| Hypoxia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 2 / 40 (5.00%) | |
| occurrences (all) | 1 | 2 | |
| Lung infiltration | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nasal congestion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Nasal disorder | | | |
| alternative assessment type: Non- | | | |

| | | | |
|---|---|---|---|
| systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nasal dryness | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Oropharyngeal pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Paranasal sinus mucosal hypertrophy | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Pharyngeal inflammation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Pulmonary oedema | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Rhinorrhoea | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sinus disorder | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Tachypnoea | | | |
| alternative assessment type: Non-systematic | | | |

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|---|---|---|---|
| subjects affected / exposed | 2 / 34 (5.88%) | 6 / 40 (15.00%) | |
| occurrences (all) | 2 | 6 | |
| Wheezing | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Psychiatric disorders | | | |
| Aggression | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Agitation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 1 / 40 (2.50%) | |
| occurrences (all) | 2 | 1 | |
| Anxiety | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Confusional state | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Hallucination | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Insomnia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Irritability | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 34 (8.82%) | 1 / 40 (2.50%) | |
| occurrences (all) | 3 | 1 | |
| Staring | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 8 / 34 (23.53%) | 6 / 40 (15.00%) | |
| occurrences (all) | 9 | 8 | |
| Aspartate aminotransferase increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 7 / 34 (20.59%) | 5 / 40 (12.50%) | |
| occurrences (all) | 9 | 8 | |
| Bacterial test positive | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Blood albumin decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Blood alkaline phosphatase increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood bicarbonate decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 2 / 40 (5.00%) | |
| occurrences (all) | 1 | 3 | |
| Blood bilirubin increased | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 34 (8.82%) | 2 / 40 (5.00%) | |
| occurrences (all) | 3 | 2 | |
| Blood creatinine increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 2 / 40 (5.00%) | |
| occurrences (all) | 1 | 2 | |
| Blood immunoglobulin G decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood lactate dehydrogenase increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Blood pressure increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Blood urea increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 3 / 40 (7.50%) | |
| occurrences (all) | 1 | 3 | |
| Chest X-ray abnormal | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| CSF virus identified | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Clostridium test positive | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 0 / 40 (0.00%) | |
| occurrences (all) | 2 | 0 | |

| | | | |
|---|---|---|---|
| Cytomegalovirus test | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Cytomegalovirus test positive | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Electrocardiogram QT prolonged | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gamma-glutamyltransferase increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 5 / 34 (14.71%) | 3 / 40 (7.50%) | |
| occurrences (all) | 6 | 3 | |
| Heart rate increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hepatic enzyme decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hepatic enzyme increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 4 / 34 (11.76%) | 3 / 40 (7.50%) | |
| occurrences (all) | 4 | 5 | |
| Human herpes virus 6 serology positive | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Liver function test abnormal | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lipase increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Oxygen saturation decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | 4 / 40 (10.00%) | |
| occurrences (all) | 3 | 4 | |
| Transaminases increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Urine output decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 3 / 40 (7.50%) | |
| occurrences (all) | 2 | 3 | |
| Viral test positive | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 2 / 40 (5.00%) | |
| occurrences (all) | 2 | 2 | |
| Visual tracking test abnormal | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Weight decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Weight increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 2 / 40 (5.00%) | |
| occurrences (all) | 1 | 2 | |

| | | | |
|---|---|---|---|
| White blood cell count decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 2 / 40 (5.00%) | |
| occurrences (all) | 1 | 2 | |
| Graft complication | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Laceration | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Joint injury | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Overdose | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Scratch | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Suture related complication | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Congenital, familial and genetic disorders | | | |

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|---|---|---|---|
| Factor VII deficiency | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac disorders | | | |
| Atrioventricular block first degree | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bradycardia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 2 / 40 (5.00%) | |
| occurrences (all) | 2 | 2 | |
| Dilatation ventricular | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Left ventricular hypertrophy | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sinus tachycardia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Tachycardia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 3 / 40 (7.50%) | |
| occurrences (all) | 1 | 3 | |
| Ventricular extrasystoles | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nervous system disorders | | | |

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|---|---|---|---|
| Burning sensation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Dizziness | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lethargy | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 0 / 40 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Headache | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | 4 / 40 (10.00%) | |
| occurrences (all) | 3 | 4 | |
| Somnolence | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 1 / 40 (2.50%) | |
| occurrences (all) | 2 | 1 | |
| Tremor | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Haemolysis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Leukocytosis | | | |
| alternative assessment type: Non-systematic | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Neutropenia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 3 / 40 (7.50%) | |
| occurrences (all) | 1 | 3 | |
| Pancytopenia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 2 / 40 (5.00%) | |
| occurrences (all) | 1 | 2 | |
| Splenomegaly | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Thrombocytopenia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 4 / 34 (11.76%) | 4 / 40 (10.00%) | |
| occurrences (all) | 4 | 5 | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 2 / 40 (5.00%) | |
| occurrences (all) | 0 | 2 | |
| Eye disorders | | | |
| Astigmatism | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blindness | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Conjunctival haemorrhage | | | |
| alternative assessment type: Non-systematic | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Colour blindness acquired | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Eye pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eye irritation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dry eye | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 3 / 40 (7.50%) | |
| occurrences (all) | 1 | 3 | |
| Eye pruritus | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lacrimation decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Myopia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Periorbital oedema | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |

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|---|---|---|---|
| Vision blurred | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Visual acuity reduced | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 0 / 40 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Abdominal distension | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 3 / 40 (7.50%) | |
| occurrences (all) | 1 | 3 | |
| Anorectal discomfort | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Abdominal pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 9 / 34 (26.47%) | 9 / 40 (22.50%) | |
| occurrences (all) | 10 | 10 | |
| Abdominal pain upper | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 2 / 40 (5.00%) | |
| occurrences (all) | 1 | 2 | |
| Ascites | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Constipation | | | |
| alternative assessment type: Non-systematic | | | |

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|---|---|---|---|
| subjects affected / exposed | 7 / 34 (20.59%) | 5 / 40 (12.50%) | |
| occurrences (all) | 7 | 5 | |
| Gastric haemorrhage | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Diarrhoea | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 6 / 34 (17.65%) | 6 / 40 (15.00%) | |
| occurrences (all) | 6 | 7 | |
| Dysphagia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastritis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 1 / 40 (2.50%) | |
| occurrences (all) | 2 | 1 | |
| Gastrooesophageal reflux disease | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 2 / 40 (5.00%) | |
| occurrences (all) | 0 | 2 | |
| Gingival bleeding | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Haematochezia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Haematemesis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 2 / 40 (5.00%) | |
| occurrences (all) | 2 | 2 | |

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|---|---|---|---|
| Gingival hypertrophy | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Lip ulceration | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lip dry | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Mouth haemorrhage | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 2 / 40 (5.00%) | |
| occurrences (all) | 1 | 2 | |
| Nausea | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 6 / 34 (17.65%) | 3 / 40 (7.50%) | |
| occurrences (all) | 6 | 4 | |
| Oral disorder | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oral pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 2 / 40 (5.00%) | |
| occurrences (all) | 2 | 2 | |
| Proctalgia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Stomatitis | | | |
| alternative assessment type: Non-systematic | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 34 (2.94%) | 3 / 40 (7.50%) | |
| occurrences (all) | 1 | 3 | |
| Vomiting | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 4 / 34 (11.76%) | 4 / 40 (10.00%) | |
| occurrences (all) | 5 | 4 | |
| Hepatobiliary disorders | | | |
| Hepatomegaly | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 3 / 40 (7.50%) | |
| occurrences (all) | 1 | 5 | |
| Hepatosplenomegaly | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 2 / 40 (5.00%) | |
| occurrences (all) | 1 | 2 | |
| Hyperbilirubinaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 4 / 34 (11.76%) | 5 / 40 (12.50%) | |
| occurrences (all) | 4 | 6 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 7 / 34 (20.59%) | 6 / 40 (15.00%) | |
| occurrences (all) | 7 | 6 | |
| Dermatitis contact | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Dry skin | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 2 / 40 (5.00%) | |
| occurrences (all) | 1 | 2 | |
| Erythema | | | |
| alternative assessment type: Non-systematic | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 2 / 34 (5.88%) | 1 / 40 (2.50%) | | |
| occurrences (all) | 2 | 1 | | |
| Papule | | | | |
| alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Pruritus | | | | |
| alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 10 / 34 (29.41%) | 12 / 40 (30.00%) | | |
| occurrences (all) | 10 | 12 | | |
| Rash | | | | |
| alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 9 / 34 (26.47%) | 8 / 40 (20.00%) | | |
| occurrences (all) | 10 | 8 | | |
| Rash erythematous | | | | |
| alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | | |
| occurrences (all) | 0 | 1 | | |
| Rash macular | | | | |
| alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 2 / 40 (5.00%) | | |
| occurrences (all) | 1 | 2 | | |
| Rash pruritic | | | | |
| alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | 1 | | |
| Rash maculo-papular | | | | |
| alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 3 / 40 (7.50%) | | |
| occurrences (all) | 3 | 3 | | |
| Skin disorder | | | | |
| alternative assessment type: Non-systematic | | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | 3 / 40 (7.50%) | | |
| occurrences (all) | 3 | 3 | | |

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|---|---|---|---|
| Skin discolouration | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin exfoliation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin lesion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin hyperpigmentation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Swelling face | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urticaria | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Renal and urinary disorders | | | |
| Bladder spasm | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Cystitis haemorrhagic | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 2 / 40 (5.00%) | |
| occurrences (all) | 2 | 2 | |
| Dysuria | | | |
| alternative assessment type: Non-systematic | | | |

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|---|---|---|---|
| subjects affected / exposed | 6 / 34 (17.65%) | 4 / 40 (10.00%) | |
| occurrences (all) | 6 | 4 | |
| Glycosuria | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Haematuria | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 4 / 34 (11.76%) | 3 / 40 (7.50%) | |
| occurrences (all) | 4 | 3 | |
| Oliguria | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 1 / 40 (2.50%) | |
| occurrences (all) | 2 | 1 | |
| Pyelocaliectasis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Renal impairment | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Urethral pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Endocrine disorders | | | |
| Cushingoid | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 2 / 40 (5.00%) | |
| occurrences (all) | 1 | 2 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| alternative assessment type: Non-systematic | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 2 | 1 | |
| Back pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 0 / 40 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Bone pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 0 / 40 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Musculoskeletal pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Groin pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Pain in extremity | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | 2 / 40 (5.00%) | |
| occurrences (all) | 4 | 2 | |
| Infections and infestations | | | |
| Alpha haemolytic streptococcal infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Bacteraemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Bacterial infection | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 34 (0.00%) | 2 / 40 (5.00%) | |
| occurrences (all) | 0 | 2 | |
| Bacterial sepsis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 0 / 40 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Clostridium difficile infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 1 / 40 (2.50%) | |
| occurrences (all) | 2 | 1 | |
| Candida infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Conjunctivitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 1 / 40 (2.50%) | |
| occurrences (all) | 2 | 1 | |
| Cystitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Cytomegalovirus infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | 2 / 40 (5.00%) | |
| occurrences (all) | 3 | 2 | |
| Cytomegalovirus viraemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | 1 / 40 (2.50%) | |
| occurrences (all) | 3 | 1 | |
| Enterococcal infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 0 / 40 (0.00%) | |
| occurrences (all) | 2 | 0 | |

| | | | |
|---|---|---|---|
| Enterococcal bacteraemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Escherichia bacteraemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Herpes virus infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastroenteritis adenovirus | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 2 / 40 (5.00%) | |
| occurrences (all) | 2 | 2 | |
| Human herpesvirus 6 infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Oral candidiasis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 4 / 34 (11.76%) | 0 / 40 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Paronychia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pneumonia cytomegaloviral | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rhinovirus infection | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Sinusitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 4 / 34 (11.76%) | 3 / 40 (7.50%) | |
| occurrences (all) | 4 | 3 | |
| Staphylococcal bacteraemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urinary tract infection staphylococcal | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Streptococcal bacteraemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Urinary tract infection viral | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Viraemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Viral rhinitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Viral upper respiratory tract infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |

| | | | |
|---|---|---|---|
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 6 / 34 (17.65%) | 5 / 40 (12.50%) | |
| occurrences (all) | 6 | 6 | |
| Fluid overload | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Fluid retention | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 5 / 34 (14.71%) | 8 / 40 (20.00%) | |
| occurrences (all) | 5 | 8 | |
| Hyperamylasaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Hypercalcaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 0 / 40 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperglycaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 5 / 34 (14.71%) | 7 / 40 (17.50%) | |
| occurrences (all) | 9 | 8 | |
| Hyperkalaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 4 / 40 (10.00%) | |
| occurrences (all) | 1 | 4 | |
| Hypermagnesaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Hypertriglyceridaemia | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 4 | 1 | |
| Hyperuricaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Hypoalbuminaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 3 / 40 (7.50%) | |
| occurrences (all) | 4 | 3 | |
| Hypocalcaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 1 / 40 (2.50%) | |
| occurrences (all) | 0 | 1 | |
| Hypomagnesaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 4 / 34 (11.76%) | 3 / 40 (7.50%) | |
| occurrences (all) | 4 | 3 | |
| Hypokalaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 34 (8.82%) | 7 / 40 (17.50%) | |
| occurrences (all) | 4 | 8 | |
| Hyponatraemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 34 (5.88%) | 2 / 40 (5.00%) | |
| occurrences (all) | 2 | 2 | |
| Hypophagia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 1 / 40 (2.50%) | |
| occurrences (all) | 1 | 1 | |
| Hypophosphataemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 34 (2.94%) | 2 / 40 (5.00%) | |
| occurrences (all) | 1 | 2 | |

| | | | |
|---|---|---|---|
| Malnutrition | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 34 (0.00%) | 2 / 40 (5.00%) | |
| occurrences (all) | 0 | 2 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported